IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re United States Patent Application of:		**Docket No.:**	**4115-150-CIP-DIV**
Applicants:	**BRYANT, Joseph, et al.**	**Conf. No.:**	**7909**
Application No.:	**10/645,451**	**Art Unit:**	**1632**
Date Filed:	**August 21, 2003**	**Examiner:**	**Marcia S. Noble**
Title:	**HIV AND CD4 TRANSGENIC ANIMALS AND USES THEREFOR**	**Customer No.:**	**23448**

DECLARATION OF DR. JOSEPH BRYANT UNDER 37 C.F.R. §1.132
IN U.S. PATENT APPLICATION NO. 10/645,451

I, Joseph L. Bryant, hereby declare that:

1. My name is Dr. Joseph L. Bryant and I am an Associate Professor with the University of Maryland School of Medicine (Baltimore, Maryland), Institute of Human Virology, and am Director of the Animal Models Division. I have received Grant/Research support on 12 separate projects and I am an author on over 45 peer-reviewed publications. I am a named inventor on U.S. Patent Application Nos. 09/058,113 (now U.S. Patent No. 6,156,952), 09/685,256 (now U.S. Patent No. 6,660,904) and 10/645,451 and Published PCT Application No. PCT/US99/07821. The University of Maryland Biotechnology Institute (UMBI) is the assignee of all rights and interests in U.S. Patent Application No. 10/293,000, as evidenced by an assignment recorded in the U.S. Patent and Trademark Office at Reel 011654, Frames 07686-90 on March 30, 2001.

2. My work at the Institute of Human Virology as the Director of the Animal Models Division includes overseeing a lab specializing in the development and analysis of animal models of various elements of chronic human viral infection and disease.

3. The invention of U.S. Patent Application No. 10/645,451 (hereinafter "the '451 application") relates to transgenic rats that express CD4 proteins on the surface of PBMCs of the transgenic rat and are capable of binding gp120. When infected with HIV, the CD4 transgenic rats exhibit symptoms of HIV infection or development of AIDS.

4. I have reviewed the Office Action mailed August 20, 2008 in the prosecution of U.S. Patent Application No. 10/645,451 and understand the rejection therein, based on 35 U.S.C. § 112, first paragraph, alleging that the pending claims fail to comply with the enablement requirement of that section.

5. Human CD4 transgenic rats have been produced by our lab according to the methods set forth in the application as discussed below and confirmed by experimental data.

6. The hCD4 transgenic rat was generated according to the specific disclosure of Example 11 of the application:

> "A rat transgenic for the human CD4 gene was prepared by inserting the human CD4 construct pLCK-CD4 described in Browning et al. (1997) *PNAS* 94: 14637 (obtained from Dr. Harris Goldstein at the Albert Einstein College of Medicine, Bronx, New York). Briefly, the construct comprises the full length coding sequence of the human CD4 gene (described in Maddon et al. (1986) *Cell* 47, 333-358) under the control of the proximal promoter for the lymphocyte specific protein tyrosine kinase p56 lck and 847 bp of simian virus 40 poly(A) tail coding sequence. The construct was linearized and used to prepare a transgenic rat as described in Example 1 with the following differences. Pseudopregnant females were obtained by synchronysing the estrous cycle of female rats with an LH-RH antagonist, [Ds-Gly10, D-Ala6, ProNHEt9]LH-RH. Mature SD 150-180g females were given 40 μg of the LH-RH agonist by ip injection at 08:00 hr on day minus 4 and placed with vasectomized males on day 0 at 15:00 hr. On the morning of day 1, the females were examined for the presence of copulatory plugs, as described above. The other difference with the method described in Example 1 is the use of R1ECM medium, described in Miyoshi et al. (1994) *Journal of Reproduction and Fertility* 100: 21, instead of medium M16.
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> "The huCD4 transgenic rat that was obtained was born with bilateral small commissures. The rat was also smaller in size as compared to a littermate control. Otherwise the rat seemed phenotypically identical to a non transgenic rat."

7. The transgenic rats were tested to establish presence of the hCD4 gene and expression of hCD4. Blood was drawn from the transgenic rats and tested for the presence of hCD4.

8. The hCD4 transgenic rat was infected with HIV-1 according to the specific disclosure of Example 11 of the application:

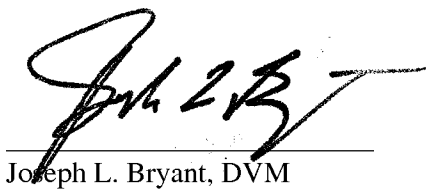
> "Infection of hCD4 transgenic rats with HIV can be performed as follows. Mature (6 to 8 weeks old transgenic rats can be inoculated either intravenously (IV) or intraperitoneally (IP) with various concentrations of HIV (IIIB) (0.1-20 $TCID_{50}$) or with 10^5 HIV-1 (IIIB)-infected CEM cells. Alternatively, the rats can be infected with a T cell tropic HIV isolate. Control animals can be non transgenic rats injected with non-infectious virus and hCD4 transgenic rats infected with the NSI HIV-1 (BA-L) or with diluted pellets from non-infected CEM cells. The presence of HIV-1 antibodies and viral antigen (p24) in the sera can then be analyzed every 2 weeks for the first two months and at 4 months post inoculation using a commercially available ELISA test. Rat PBMCs can be isolated on Ficoll-hypaque and 1.0 x 10^6 cells can be cultured with 0.3 x 10^6 CEM cells. Simultaneously, 10^6 PBMC can be treated with 3 µg/ml of PHA overnight and then cultured with CEM. Cultures can be examined for CPE for 1 month and supernatant can be checked for antigen production by ELISA weekly."

9. Furthermore, the hCD4 transgenic rat was used to generate a double transgenic rat, CD4xHIV-1, as claimed in related U.S. Patent Application No. 09/685,256, now U.S. Patent No. 6,660,904.

10. The resulting hCD4 transgenic rats are being utilized by our lab, as described in the application, in the identification of drugs for treating or preventing other CD4-related diseases and immune disorders.

11. Taken together, these results show that by following the methods set forth in the present application, a CD4 transgenic rat was produced and used, in accordance with methods set forth in the application.

As the below-named declarant, I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that willful false statements, and the like, so made are punishable by fine or imprisonment, or both, under Section 1001 or Title 18 of the United States Code and that such willful false statements may jeopardize the validity of United States Patent Application No. 10/645,451 or any patent issued thereon.



Joseph L. Bryant, DVM